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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte SHAKER A. MOUSA,
Appellant[1]

Appeal 2010-003549
Application 10/667,216
Technology Center 1600

Before CAROL A. SPIEGEL, FRANCISCO C. PRATS, and
JEFFREY N. FREDMAN, *Administrative Patent Judges*.

SPIEGEL, *Administrative Patent Judge.*

DECISION ON APPEAL[2]

Appellant appeals under 35 U.S.C. § 134(a) from an Examiner's rejection of claims 1, 2, 5, 6, 43, 49-54, 56-59, 61-62, and 91-94 (App. Br. 1-2; Ans. 2).[3] The Examiner has not rejected claim 63 as unpatentable.

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[1] The assignee of record is Vascular Vision Pharmaceuticals, Inc. (Patent Assignment Abstract of Title Reel/Frame 014843/0315, recorded 2 January 2004).

[2] The two-month period for filing an appeal or commencing a civil action, as recited in 37 C.F.R. § 1.304, or for filing a request for rehearing, as recited in 37 C.F.R. § 41.52, begins to run from the "MAIL DATE" (paper delivery mode) or the "NOTIFICATION DATE" (electronic delivery mode) shown on the PTOL-90A cover letter attached to this decision.

[3] This decision cites the Brief of Appellant filed 7 July 2009 ("App. Br."), the Reply Brief of Appellant filed 28 December 2009 ("Reply Br."), the

Claims 64-90, the only other pending claims, stand withdrawn from consideration as drawn to a non-elected invention. We have jurisdiction under 35 U.S.C. § 134. We AFFIRM.

I. Statement of the Case

The subject matter on appeal is directed to oxidized, supersulfated heparin fractions having molecular weights from about 2 to about 4 kDa and reduced anticoagulant and anti-angiogenesis properties. Claims 1, 91-93, 43, 56, and 94 are illustrative and read (App. Br. 47-52):

> 1. An oxidized heparin fraction having a molecular weight of from about 2,000 to about 4,000 daltons,
>
> wherein the oxidized heparin fraction is super-sulfated such that the super-sulfated oxidized heparin fraction comprises an anticoagulant reduction characteristic and an angiogenesis inhibition characteristic;
>
> wherein the super-sulfated oxidized heparin fraction has a chemical structure of a first oxidized heparin fraction after the first oxidized heparin fraction has been O-sulfated by sulfate substitution at oxygen bonds within repeating units of the first oxidized heparin fraction;
>
> wherein the super-sulfated oxidized heparin fraction fully inhibits fibroblast growth factor (FGF2) induced angiogenesis.
>
> 91. The oxidized heparin fraction of claim 1, wherein the super-sulfated oxidized heparin fraction comprises a sulfate to carboxylate ratio of about 5:1.
>
> 92. The oxidized heparin fraction of claim 1, wherein from about 50% to about 100% of primary hydroxyls in glucosamine residues and secondary hydroxyl groups in disaccharide units are substituted by O-sulfate esters in the O-sulfated oxidized heparin fraction.
>
> 93. The oxidized heparin fraction of claim 1,

Examiner's Answer mailed 27 October 2009 ("Ans."), and the Specification ("Spec.") of Application 10/667,216 ("the 216 Application").

wherein the anticoagulant reduction characteristic comprises a first anticoagulant reduction characteristic, a second anticoagulant reduction characteristic, or a combination thereof;

wherein the first anticoagulant reduction characteristic is that the oxidized heparin fraction reduces a mean percent inhibition of platelet clot strength by [a] factor of at least about 8 relative to a mean percent inhibition of platelet clot strength of unfractionated heparin under a condition of the concentration of the oxidized heparin fraction in human blood being equal to the concentration of the unfractionated heparin in human blood;

wherein the second anticoagulant reduction characteristic is that the oxidized heparin fraction reduces a prolongation of clotting time of human blood by at least 75% relative to a prolongation of clotting time of human blood by unfractionated heparin under a condition of the concentration of the oxidized heparin fraction in human blood being equal to the concentration of the unfractionated heparin in human blood, subject to the clotting time being a prothrombin time (PT) or an activated partial thromboplastin time (APTT); and

wherein the angiogenesis inhibition characteristic is that the oxidized heparin fraction in an endothelial cell (EC) growth medium cancels an effect of recombinant human fibroblast growth factor (FGF2) on EC tube formation in the EC growth medium under a condition of the concentration of FGF2 in the EC growth medium being sufficient to increase a length or area of the EC tube formation by a factor of at least about 2 if the oxidized heparin fraction is not in the EC growth medium.

43. A composition comprising from about 60% to about 100% of the oxidized heparin fraction of claim 1, and from about 0% to about 40% of heparin, low molecular weight heparin, chondroitin sulfates, dermatan sulfates, heparan [sic] sulfates, heparin derivatives, or combinations thereof.

56. A polymeric structure comprising the oxidized heparin fraction of claim 1, wherein said oxidized heparin fraction is covalently attached to the polymeric structure by surface grafting or copolymerization, non-covalently incorporated into

> a matrix of the polymeric structure, or encapsulated as a biomedical material within the polymeric structure.
>
> 94. A method, comprising forming the oxidized heparin fraction of claim 1, wherein said forming the oxidized heparin fraction comprises O-sulfating the first oxidized heparin fraction by performing sulfate substitution at oxygen bonds within repeating units of the first oxidized heparin fraction.

The Examiner rejected some claims as anticipated and others as obvious.[4] We begin with the anticipation rejection.

II. Anticipation

A. Statement of the rejection

The Examiner rejected claims 1, 2, 5, 6, 43, and 91-94 under 35 U.S.C. § 102(b) as anticipated by Naggi[5] in light of the MGH APTT and Anti-Xa Assays[6, 7] (Ans. 5-9).

Briefly, the Examiner found that the claimed oxidized supersulfated heparin fraction (hereinafter "the claimed heparin fraction") reads on the depolymerized supersulfated heparin of Naggi formula IV wherein A is H or

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[4] The Examiner withdrew the prior rejections of claims 1, 2, 5, 6, 43, 49-54, 56-59, 61-63, and 91-94 under 35 U.S.C. § 112, first paragraph, set forth on pages 2-11 of the Office action mailed 27 October 2008 (Ans. 3-4).

[5] US Patent 4,727,063, *Depolymerized and Supersulfated Heparin, Process for its Preparation and Pharmaceutical Compositions*, issued 23 February 1988 to Naggi et al. ("Naggi").

[6] Massachusetts General Hospital Activated Partial Thromboplastin Time Assay Brochure downloaded from http://www.massgeneral.org/pathology/coagbook/CO003400.htm on 20 October 2008 ("MGH APTT Assay").

[7] Massachusetts General Hospital Heparin Antifactor Xa Assay Brochure downloaded from http://www.massgeneral.org/pathology/coagbook/co005000.htm on 20 October 2008 ("MGH Anti-Xa Assay").

SO_3^-, B is SO_3^- or $COCH_3$, and m is an integer from 4 to 15 and having a sulfation degree of at least 2.5 (hereinafter "Naggi's heparin fraction") formed by treating a starting heparin with sulfuric acid and chlorosulfonic acid, a strong oxidizing agent (Ans. 5-6, 15-20). The Examiner found that Naggi's heparin fraction has an anticoagulant reduction characteristic based on reduced APTT and Anti-factor Xa results (*id.* at 6-7), a sulfate-to-carboxylate ratio of *about* 5:1 based on a disclosed ratios of 2.6:1, for example (*id.* at 5-6, 19-20), and pharmaceutical compositions comprising Naggi's heparin fraction, e.g., in amounts up to about 100% (*id.* at 6, 20).

The Examiner acknowledges that Naggi is silent regarding its heparin fraction's angiogenesis inhibition characteristic, including inhibition of FGF2-induced angiogenesis, and measuring anticoagulant reduction characteristic by a clot strength assay (*id.* at 7, 15). However, based on the results of APTT and Anti-factor Xa assays disclosed by Naggi and the structural identity between the claimed heparin fraction and Naggi's heparin fraction, the Examiner believes that these two limitations are inherent characteristics of Naggi's heparin fraction (*id.* 8, 15-19).

Appellant argues each of claims 1, 2, 5, 6, 43, and 91-94 separately (App. Br. 20-36).[8] Specifically, as to claim 1, Appellant argues that Naggi's method of generating an oxidized supersulfated heparin fraction differs from Appellant's method and, therefore, the claimed heparin fraction and Naggi's heparin fraction are different (App. Br. 20, 22-24). Thus, Appellant asserts

[8] Appellant refers to an article by Lundin on page 21 of the Appeal Brief. We have not considered arguments based on Lundin because, according to Appellant, "[t]here is no evidence entered by the Examiner and relied upon by Appellant[] in this appeal" (App. Br. 53) and because the Examiner did not discuss Lundin in his Answer.

that Naggi's heparin fraction does not fully inhibit FGF2-induced angiogenesis in the absence of experimental proof (*id.* at 21). Appellant further argues that the APTT results in Table 1 of Naggi is expressed in U/ml, not in units of clotting time, and, thus, fails to disclose a heparin fraction that "reduces a prolongation of clotting time" as recited in claims 5, 6, and 93 (*id.* at 26-27, 29-33). Appellant contends that the Examiner failed to provide evidence to support his allegation that Naggi's heparin fraction cancels the effect of recombinant FGF2 on endothelial cell formation as recited in claim 93 (*id.* at 27). Appellant further contends that Naggi's teaching that its heparin fraction shows a weak anticoagulant activity does not inherently disclose that Naggi's heparin fraction reduces a mean percent inhibition of platelet strength clot strength by a factor of at least 8 vis-à-vis unfractionated heparin as recited in claims 2, 6, and 93 (*id.* at 28-29, 31-33). As to claim 91, Appellant argues that a sulfate to carboxylate ratio of about 5:1 does not encompass a 2.6:1 because 5:1 is more than 90% higher than 2.6 (*id.* at 34). Appellant further argues that the Examiner fails to allege that "about 50% to about 100% of primary hydroxyls in glucosamine residues and secondary hydroxyl groups in disaccharide units are substituted by O-sulfate esters in the O-sulfated oxidized heparin fraction," as recited in claim 92, is even disclosed by Naggi (*id.* at 34). Appellant also argues that the Examiner has failed to provide evidence that intermediate structures recited in claim 94 are produced by Naggi's method of generating Naggi's heparin fraction (*id.* at 35-36). Finally, Appellant argues that a teaching of pharmaceutical compositions containing Naggi's heparin fraction as an active agent fails to teach a "composition comprising from about 60% to about 100% of the oxidized heparin fraction," as recited in claim 43 (*id.* at

36). These arguments are reiterated in Appellant's Reply Brief (Reply Br. 2-20).

Thus, at issue is whether the Examiner has factually established a basis for finding that Naggi expressly or inherently discloses each and every limitation of claims 1, 2, 5, 6, 43, and 91-94.

B. Finding of fact

The following findings of fact ("FF") are supported by a preponderance of the evidence of record.

1. Application 10/667,216

[1] According to the instant Specification, oxidizing agents "including, but not limited to, periodic acid, metals in high valence states, halogens, halogen atoms, and compounds with O-O bonds, such as O_3, diacyl peroxides, H_2O_2, and O_2" may be used to oxidize heparin fractions (Spec. 8, ¶ 26).

[2] Oxidized heparin fractions may be chemically enriched with sulfate groups, e.g., by treatment with sulfur trioxide, prior to or after oxidation (*id.* at 9-10, ¶ 29; 21-23, ¶¶ 60-65 (Examples 2-3)).

[3] Alternatively, commercially available high sulfate heparin may be used as a starting material for oxidation (*id.* at 9-10, ¶ 29).

[4] According to the Specification,

> [i]n one embodiment …, the oxidized heparin fraction comprises constituents having a high sulfate to carboxylate ratio. … [A] high sulfate to carboxylate ratio ranges from about 2:1 to about 5:1. In a preferred embodiment, from about 50% to about 100% of primary hydroxyls in glucosamine residues and secondary hydroxyl groups in disaccharide units are substituted by O-sulfate esters. (*Id.* at 9, ¶ 29).

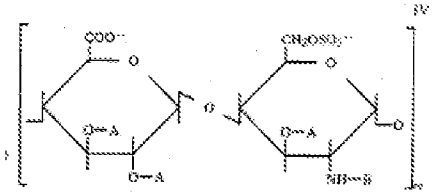
2. Naggi

[5] Naggi treats an unfractionated or "starting" heparin with a mixture of sulfuric acid and chlorosulfonic acid, i.e., oxidizing agents, to produce a depolymerized supersulfated heparin fraction having a molecular weight between 2 and 9 kDa, a degree of sulfation at least 20% higher than that of the starting heparin, and possessing a weak anticoagulant activity (Naggi 3:52-53; 4:66-5:2; 5:42-52).

[1] Naggi uses ultrafiltration to separate out a heparin fraction of a desired molecular weight (*id.* at 8:6-9).

[2] According to Naggi, "the primary hydroxy groups at the 6-position of all the glucosamine subunits are esterified by a sulfate group and … at least the hydroxy group in the 3-position of the glucosamine residue … is extensively sulfated" (*id.* at 5:24-30).

[3] Specifically, Naggi's heparin fraction has a structure of formula IV:



wherein A is H or SO_3^-, B is SO_3^- or $COCH_3$, and m is an integer from 4 to 15 (*id.* at 2:13-14; 5:66-6:14).

[4] Preferably,

> B is a $COCH_3$ group in 0 to about 30% of the m disaccharide units, according to the percent of acetyl groups existing in the commercial heparin from which the supersulfated heparin derives, and a SO_3^- group in the remaining disaccharide units; the substituent A in the position 3 of the glucosamine subunit is SO_3^- in at least 50% of the m disaccharide units and hydrogen in the

> remaining ones; the substituent A in the position 2 of the uronic acid subunit is SO_3^- in at least 70% of the m disaccharide units and hydrogen in the remaining ones; the substituent A in the position 3 of the uronic acid subunit is prevalently hydrogen, but it can be SO_3^- in some of the m disaccharide units. [*Id.* at 6:36-53.]

[5] Naggi's heparin fraction has a degree of sulfation of at least 2.5, preferably from 3.0±0.1 to 3.3±0.1 (*id.* at 5:58-63; 6:54-57).

[6] The Naggi heparin fraction described in Example 2 has a molecular weight of 3 to 5 kDa and a sulfation degree of 2.6 (*id.* at 12:1-30).

[7] Naggi quantitated the effect of its heparin fractions on blood coagulation by determining the ratio of their activity towards factor Xa (anti-Xa activity) and Activated Partial Thromboplastin Time (APTT; extrinsic total coagulation) (*id.* at 9:7-11).

[8] According to Naggi, factor Xa is responsible for transforming prothrombin into thrombin and, therefore, anti-Xa action prevents formation of circulating thrombin (*id.* at 9:12-15).

[9] Further according to Naggi, APTT measures all of the factors in the extrinsic pathway, factor Xa included, and is an indirect measure of hemorrhagic risk (*id.* at 9:15-19).

[10] According to the data in Tables I and II, the Naggi heparin fractions presented less hemorrhagic risk than their corresponding starting heparins, i.e., gave a lower APTT result, and interfered less with formation of circulating thrombin, i.e., gave a lower anti-Xa activity result (*id.* at 9:48-10:16).

[11] According to Naggi, the anti-Xa and APTT assays are conventional techniques for evaluating whole blood coagulation, citing Yin et al.,

J. Lab. Clin. Med. 1973, 81, 298-310, and Proctor and Rapaporti, Am. J. Clin. Pathol., 1961, 36, 212, respectively (*id.* at 9:39-46).

[12] The MGH Anti-Xa assay is a chromogenic enzyme test used to determine if a patient is at the desired level of anticoagulation with therapeutic doses of heparin, low molecular weight heparin, or danaparoid (MGH Anti-Xa Assay 2). Results are reported as anticoagulant concentration in anti-Xa units/mL, such that high anti-Xa values indicate high levels of anticoagulation and low anti-Xa values indicate low levels of anticoagulation (*id.*).

[13] The MGH APTT assay measures the clotting time from the activation of factor XII, through the formation of a fibrin clot (MGH APTT Assay 1) to screen the integrity of the intrinsic pathway of coagulation (factors VIII, IX, XI, and XII) and to a lesser extent the common pathway (fibrinogen and factors II, V, and X) (*id.* at 2). Anticoagulants, such as heparin, prolong the clotting time (*id.* at 1).

[14] Naggi teaches providing pharmaceutical compositions containing its heparin fraction as an active ingredient (*id.* at 10:54-57).

Other findings of fact follow below.

C. Legal principles

During examination of a patent application, a claim is given its broadest reasonable construction consistent with the specification. *In re Prater*, 415 F.2d 1393, 1404-05 (CCPA 1969).

It is well settled that when a claimed product or process reasonably appears to be substantially the same as a product or process disclosed by the prior art, the burden is properly upon the applicant to demonstrate that the prior art product or process does not necessarily or inherently possess

characteristics attributed to the claimed product or process. *In re Spada*, 911 F.2d 705, 708 (Fed. Cir. 1990); *In re Best*, 562 F.2d 1252, 1255 (CCPA 1977). Objective evidence to the contrary is required to rebut the reasonable presumption. *In re Spada,* 911 F.2d at 708; *In re Best,* 562 F.2d at 1255.

D. Analysis

Claim 1 recites an oxidized heparin fraction that is supersulfated and has a molecular weight of about 2 to 4 kDa. Naggi's heparin fraction is obtained by treating a starting heparin with a mixture of sulfuric acid and chlorosulfonic acid, known oxidizing agents, to produce supersulfated heparin fractions having a molecular weight between 2 and 9 kDa, e.g., the 3 to 5 kDa molecular weight Naggi heparin fraction of Example 2 (FF 5-6). Neither the instant Specification nor the claims require using specific oxidizing agents to oxidize starting heparin materials or performing oxidation and sulfation in any particular order (see e.g., FF 1-3). Moreover, claim 1 is not a product-by-process claim. Regardless, it is well settled that the patentability of a product-by-process claim is based on the product itself. *In re Stephens*, 345 F.2d 1020, 1023 (CCPA 1965). Furthermore, the claimed heparin fractions include oxidized heparin fractions with a high sulfate to carboxylate ratio, e.g., ranging from about 2:1 to about 5:1 (FF 4). Naggi's heparin fraction has a sulfate to carboxylate ratio of at least 2.5 (FF 5). Claim 1 also requires the claimed heparin fraction to be a less potent anticoagulant than the starting heparin from which it is made (see claim 93 for an explanation of "an anticoagulant reduction characteristic"). Naggi's heparin fraction has a weak anticoagulant activity (FF 5) as demonstrated by its lower anti-Xa activity and lower APTT vis-à-vis its respective starting heparin (FF 7, 10). Thus, the Examiner has provided a sufficient factual

basis for reasonably believing that Naggi's heparin fraction and the claimed heparin fraction are the same or substantially the same compound.

Claim 1 also requires the claimed heparin fraction to inhibit angiogenesis, specifically to fully inhibit FGF2-induced angiogenesis. Naggi is silent on the angiogenesis inhibiting properties of its heparin fraction. However, when a claimed product reasonably appears to be identical or substantially identical as a product disclosed by the prior art, the burden is properly upon the applicant to demonstrate that the prior art product or process does not necessarily or inherently possess characteristics attributed to the claimed product or process. *In re Spada*, 911 F.2d at 708; *In re Best*, 562 F.2d at 1255. The fairness of shifting the burden of proof to the Appellant at this point is evidenced by the PTO's inability to manufacture products or to obtain and compare prior art products. *In re Best*, 562 F.2d at 1255.

It is also fair to shift the burden of proof to Appellant to show that Naggi's heparin fraction does not inherently "reduce[] a mean percent inhibition of platelet clot strength by [a] factor of at least about 8 relative to a mean percent inhibition of platelet clot strength of unfractionated heparin under a condition of the concentration of the oxidized heparin fraction in human blood being equal to the concentration of the unfractionated heparin in human blood," as recited by claims 2, 6, and 93. Naggi states and demonstrates that its heparin fraction has reduced anticoagulant activity vis-à-vis its corresponding starting (unfractionated) heparin (FF 5, 10). The evidence of record suggests that there are number of conventional techniques used in the art for testing anticoagulant activity, including APTT and anti-factor Xa assays (FF 7, 11-13). It is fair to shift the burden of proof

to Appellant to show that Naggi's heparin fraction does not have reduced anticoagulant activity vis-à-vis its corresponding starting heparin using the particular technique for testing anticoagulant activity chosen by Appellant and recited in claims 2, 6, and 93. The fairness of shifting the burden of proof to the Appellant at this point is evidenced by the PTO's inability to manufacture products or to obtain and compare prior art products. *In re Best*, 562 F.2d at 1255.

For the same reasons, we find that the Examiner has provided a sufficient factual basis to shift the burden of proof to the Appellant to show that Naggi's heparin fractions do not "reduce[] a prolongation of clotting time of human blood by at least 75% relative to a prolongation of clotting time of human blood by unfractionated heparin under a condition of the concentration of the oxidized heparin fraction in human blood being equal to the concentration of the unfractionated heparin in human blood, subject to the clotting time being a prothrombin time (PT) or an activated partial thromboplastin time (APTT)," as recited in claims 5, 6, and 93. Since, as noted by Appellant (App. Br. 26-27), Naggi did not report the results of its APTT assay in seconds, it would be improper to assume that Naggi used the same APTT test method as Appellant. Similarly, as stated above in regard to claim 1, we find that the burden of proof has also shifted to Appellant to show that Naggi's heparin fraction does not inherently, "in an endothelial cell (EC) growth medium cancel[] an effect of recombinant human fibroblast growth factor (FGF2) on EC tube formation in the EC growth medium under a condition of the concentration of FGF2 in the EC growth medium being sufficient to increase a length or area of the EC tube formation by a factor of

at least about 2 if the oxidized heparin fraction is not in the EC growth medium," as recited in claim 93.

As noted by the Examiner (Ans. 6, 19), the instant Specification does not define the term "about" as recited in claim 91. Therefore, we agree with the Examiner that a supersulfated sulfate to carboxylate ratio of "about" 5:1, i.e., a sulfation degree of 5, reasonably reads on a sulfation degree of at least 2.5, such as the 2.6 of Naggi Example 2 (FF 5-6). In other the words, the claimed sulfation degree of 5 is less than twice the lowest permissible sulfation degree disclosed by Naggi (*id.*).

Appellant argues that Naggi fails to disclose a heparin fraction "wherein from about 50% to about 100% of primary hydroxyls in glucosamine residues and secondary hydroxyl groups in disaccharide units are substituted by O-sulfate esters in the O-sulfated oxidized heparin fraction," as recited by claim 92. Appellant does not dispute the Examiner's statement that Naggi discloses "a heparin fraction wherein 52% of the primary and secondary hydroxyl groups are substituted by O-sulfate esters" (Ans. 6, 19). Rather, Appellant argues that the Examiner's statement "does not address the limitations of the substitutions by 0-sulfate [sic] esters occurring at hydroxyl groups in *glucosamine residues* and in *disaccharide* units" (Reply Br. 17, original emphasis). However, formula IV of Naggi expressly depicts Naggi's heparin fraction as a polymer of disaccharide units consisting of glucuronic acid and glucosamine subunits and expressly shows 100% of the primary hydroxyl groups at the 6-position of all glucosamine subunits esterified by a sulfate group (FF 2-3). Claim 92 does not require any particular ratio of O-sulfated primary hydroxyl groups to O-sulfated hydroxyl groups. Therefore, this argument is not persuasive of patentability.

As to claim 94, the Examiner has provided a reasoned basis for believing that the recited intermediate structures were inherent in the method described for producing Naggi's heparin fractions (see Ans. 6). Regardless, it is well settled that the patentability of a product-by-process claim is based on the product itself. *In re Stephens*, 345 F.2d at 1023. Furthermore, Appellant has not alleged unexpected results or properties based on preparing the claimed heparin product by a specific series of method steps, e.g., first oxidizing an unfractionated heparin and then enriching with sulfate groups. Rather, the instant Specification is quite clear that oxidation and sulfation may occur in either order (FF 2). Therefore, this argument is not persuasive of patentability.

Finally, Appellant argues that Naggi fails to disclose a pharmaceutical composition "comprising from about 60% to about 100% of the oxidized heparin fraction of claim 1, and from about 0% to about 40% of heparin, low molecular weight heparin, chondroitin sulfates, dermatan sulfates, heparan sulfates, heparin derivatives, or combinations thereof," as recited in claim 43. Contrary to Appellant's argument (see e.g., Reply Br. 20), the limitations of claim 43 are met by a composition comprising about 100% of Naggi's heparin fraction and about 0% of the other components recited in claim 43. Therefore, this argument is not persuasive of patentability.

E. Conclusion

Therefore, we sustain the rejection of claims 1, 2, 5, 6, 43, and 91-94 under 35 U.S.C. § 102(b) as anticipated by Naggi in light of the MGH APTT and Anti-Xa Assays. The Examiner has established a sufficient factual basis for finding that Naggi expressly or inherently discloses each and every limitation of claims 1, 2, 5, 6, 43, and 91-94.

III. Obviousness

A. Statement of the rejection

The Examiner has rejected

(i) claims 1, 43, 49, and 50 under 35 U.S.C. § 103(a) as obvious over Naggi, as applied to claims 1 and 43, and further in view of Weitz,[9]

(ii) claims 1 and 56-59 under 35 U.S.C. § 103(a) as obvious over Naggi, as applied to claim 1, and further in view of Conrad,[10]

(iii) claims 1, 43, and 51-54 under 35 U.S.C. § 103(a) as obvious over Naggi, as applied to claims 1 and 43, and further in view of Conrad and Kerbel,[11] and

(iv) claims 1, 56, 61, and 62 under 35 U.S.C. § 103(a) as obvious over Naggi, as applied to claim 1, and further in view of Scholander[12] (Ans. 9-14).

The Examiner's findings of Naggi's disclosure in regard to claims 1 and 43 have been discussed above.

As to claims 49 and 50, the Examiner found that Naggi failed to disclose a composition comprising a non-heparin anticoagulant, e.g., an anti-Xa compound, an anti-IIa compound, an anti-tissue factor compound, and/or an anti-VIIa compound. The Examiner found that Weitz "teaches the use of

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[9] US Patent 6,075,013, *Modified Low Molecular Weight Heparin that Inhibits Clot Associated Coagulation Factors*, issued 13 June 2000 to Weitz et al. ("Weitz").

[10] US Patent 5,280,016, *Non-Anticoagulant Heparin Derivatives*, issued 18 January 1994 to Conrad et al. ("Conrad").

[11] Kerbel et al., *Possible mechanisms of acquired resistance to anti-angiogenic drugs: Implications for the use of combination therapy approaches*, 20 CANCER AND METASTASIS REVIEWS 79-86 (2001) ("Kerbel").

[12] US Patent 6,461,665 B1, *Process for Preparing Surface Modification Substances*, issued 8 October 2002 to Elisabeth Scholander ("Scholander").

modified low molecular weight heparin (column 10, lines 25-30) obtained by oxidation (column 10, lines 47-53) used in conjunction with conventional thrombolytic treatments, such as tissue plasminogen activator [tPA], an anti-tissue factor compound (column 11, lines 20-30)" (Ans. 9). Thus, the Examiner concluded that it would have been obvious to combine Naggi's heparin fraction in conjunction with conventional thrombolytic treatments, such as the anti-tissue factor compound tPA, as taught by Weitz, in order to form a third composition useful for the same purpose as an antithrombotic composition (*id.* at 9-10).

As to claims 56-59, the Examiner found that Naggi failed to disclose a polymeric structure comprising Naggi's heparin fraction covalently attached to the polymeric structure by surface grafting or copolymerization, non-covalently incorporated into a matrix of the polymeric structure, or encapsulated as a biomedical material within the polymeric structure, particularly wherein the polymeric structure is biocompatible ethylene vinyl acetate (*id.*). The Examiner found that Conrad

> teaches size separated fractions of depolymerized low molecular weight heparin produced by periodate oxidation (column 3, lines 25-29) that are non-anticoagulant and show antiproliferative activity with respect to smooth muscle cells (abstract), or an angiogenesis inhibition characteristic. Conrad … teaches that size separated fractions are treated chemically to produce O-oversulfation to increase activity (column 4, lines 27-37). Conrad … teaches the heparin administered in the form of an implant containing biodegradable polymer materials such as collagen, formulated as patches or beads, which is encapsulation [sic, encapsulated] as a biomedical material, or by local administration through a continuous release device such as a supporting matrix, which is understood to be non-covalent incorporation into the matrix (column 10, lines 47-50 and 60-63). Conrad … teaches the use of the specific polymer ethylene

> vinyl acetate as the supporting matrix (column 14, lines 34-38). [*Id.* at 10-11.]

The Examiner concluded that it would have been obvious to combine Naggi's heparin fraction with the O-oversulfated low molecular weight heparin incorporated into a polymeric structure as taught by Conrad and "use of a known technique of supersulfation to improve similar depolymerized low molecular weight heparin in the same way by combining the depolymerized and supersulfated heparin disclosed by Naggi … with the O-oversulfated low molecular weight heparin incorporated into a polymeric structure as taught by Conrad …" (*id.* at11).

As to claims 51-54, the Examiner found that neither Naggi nor Conrad discloses a composition comprising a non-heparin angiogenic inhibitor, such as interferon, thalidomide, or interleukin-12, or a cytotoxic or chemotherapeutic agent, such as microtubule agents (*id.* at 12). The Examiner found that Kerbel teaches

> the use of combinations of angiogenesis inhibitors (page 82, right column, lines 9-11), such as chemotherapy drugs such as microtubule agents and anti-angiogenic drugs (page 82, right column, lines 14-17). Kerbel … teaches the use of combinations of specific drugs such as DC101 antibody to VEGF (vascular endothelial growth factor) receptor-2 (page 83, spanning left column line 23 and right column lines 1-2); thalidomide, interferon alpha, and low molecular weight heparin (page 83, right column, lines 18-22) and angiostatin, endostatin, and interleukin-12 (page 84, left column, lines 1-3). [*Id.*]

The Examiner concluded that it would have been obvious to combine Naggi's heparin fraction in view of Conrad with the combinations of angiogenesis inhibitors taught by Kerbel to create a third composition for the

same intended purpose (*id.* at 12-13), i.e., to provide an anti-angiogenic composition.

As to claims 56, 61, and 62, the Examiner found that Naggi failed to disclose a polymeric structure wherein the oxidized heparin fraction is covalently attached to the polymeric structure by surface grafting or by copolymerization (*id.* at 13). The Examiner found that Scholander teaches

> a surface modified to have improved antithrombogenic activity by attaching heparin to the surface to be modified (abstract), comprising reacting heparin with the surface (column 4, lines 25-40), or surface grafting, or by reacting the heparin with a polymer layer and reacting the heparin-containing polymer with other polymers (column 5, lines 1-30), such as when the heparin is reacted with the later from step (a). The reaction of a heparin-containing polymer with other polymers can be interpreted as copolymerization. [*Id.* at 13-14.]

The Examiner concluded that it would have been obvious to combine Naggi's heparin fraction with a surface modified to have improved antithrombogenic activity as taught by Scholander to provide improved activity because "Naggi … recites 'It is also generally recognized that at the same degree of polymerization, the biological activity of polysaccharides increases with their sulfation degree,' (column 3, lines 42-44)" (*id.* at 14).

In response to obviousness rejections (i) and (iii), Appellant relies on his arguments above as to why Naggi does not teach or suggest all of the features of claims 1 and 43 (App. Br. 37-38, 41-43). In response to obviousness rejections (ii) and (iv), Appellant relies on his arguments above as to why Naggi does not teach or suggest all of the limitations of claim 1 (*id.* at 39-40, 44-45).

B. Discussion

Appellant does not contest the Examiner's fact finding in regard to Weitz, Conrad, Kerbel, or Scholander. According to Appellant, the patentability of claims 49-54, 56-59, 61, and 62, stand or fall with the patentability of claim 1 or 43, from which they depend. Claims 1 and 43 are not anticipated by Naggi for the reasons given above. Therefore, we sustain obviousness rejections (i) through (iv) above.

IV. Order

Upon consideration of the record, and for the reasons given, it is

ORDERED that the decision of the Examiner to reject claims 1, 2, 5, 6, 43, and 91-94 under 35 U.S.C. § 102(b) as anticipated by Naggi in light of the MGH APTT and Anti-Xa Assays is AFFIRMED;

FURTHER ORDERED that the decision of the Examiner to reject claims 1, 43, 49, and 50 under 35 U.S.C. § 103(a) as obvious over Naggi, as applied to claims 1 and 43, and further in view of Weitz, is AFFIRMED;

FURTHER ORDERED that the decision of the Examiner to reject claims 1 and 56-59 under 35 U.S.C. § 103(a) as obvious over Naggi, as applied to claim 1, and further in view of Conrad, is AFFIRMED;

FURTHER ORDERED that the decision of the Examiner to reject claims 1, 43, and 51-54 under 35 U.S.C. § 103(a) as obvious over Naggi, as applied to claims 1 and 43, and further in view of Conrad and Kerbel, is AFFIRMED;

FURTHER ORDERED that the decision of the Examiner to reject claims 1, 56, 61, and 62 under 35 U.S.C. § 103(a) as obvious over Naggi, as applied to claim 1, and further in view of Scholander is AFFIRMED; and,

FURTHER ORDERED that no time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a)(1)(iv).

AFFIRMED

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